Early Loading of Bone Anchored Hearing Implants

Clinical Evaluation of Implant Stability and Soft Tissue Reactions

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Publication date:
2019

Document Version
Publisher's PDF, also known as Version of record

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CLINICAL EVALUATION OF IMPLANT STABILITY AND SOFT TISSUE COMPLICATIONS

BY
MORTEN HØGSBRO

DISSERTATION SUBMITTED 2019

AALBORG UNIVERSITY
DENMARK

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by

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Dissertation submitted

Dissertation submitted: April 12, 2019

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ISSN (online): 2246-1302
ISBN (online): 978-87-7210-430-0

Published by:
Aalborg University Press
Langagervej 2
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Rosendahls, 2019

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ENGLISH SUMMARY

Bone anchored hearing implant surgery is a relatively new discipline within the field of otology. Implanting a titanium screw in the scull bone behind the ear and attaching a vibrating sound processor enables certain patients with a conductive hearing loss to obtain hearing rehabilitation via bone conducted sounds to the inner ear. Since 1977, when the first implantation was performed, the surgical technique and implant design have evolved side by side with the common aim of obtaining a fully osseointegrated implant without inflammation and infection in the surrounding skin. An important factor for a long lasting successful implantation is the timing of the loading of the hearing processor onto the implant since the presence of the processor and the patient handling thereof might disturb the osseointegration and increase skin inflammation. This thesis examines whether an early loading time compromises osseointegration and leads to more skin related problems. The thesis also addresses whether different types of implantation surgery lead to different results regarding osseointegration and skin related issues.

The thesis is based on two clinical studies and one laboratory study. The clinical studies comprised of one randomized clinical trial and one prospective cohort study that were published in four peer-reviewed papers in a highly esteemed international journal. The laboratory study investigated certain aspects of one of the key measurement techniques used in the clinical studies based on a temporal bone model and a plaster model.

Paper 1 and paper 2 report on the randomized clinical trial. Paper 1 reports on the part of the trial that examined the stability and osseointegration of the implants. It was shown that a healing time of two weeks instead of the consensus based 4-6 weeks was safe with regard to implant stability. Paper 2 examines the influence on skin related issues of performing implant surgery without performing reduction of the soft tissue around the implant which was thought to be essential in reducing the amount of skin inflammation around the implant. It was shown that the complication rate was lower in the group where soft tissue reduction was not performed.

Paper 3 and 4 report on a study of a new implant design where a hydroxyapatite surface coating was added to the part of the implant interacting with the skin. This coating was hypothesized to be able to reduce the rate of soft tissue complications by enabling a strong adherence between implant and soft tissue thereby hindering bacterial colonization to form in the interface. No reduction in complication rate was found for this implant system thus indicating no positive effect from the surface coating. However, these findings may have been slightly confounded by a negative effect from the loading time of only one week which may have overshadowed a possible positive effect from the abutment coating. The loading time of one week was found safe with regard to the stability of the implant.

Paper 5 reports the detailed measurements of the dependency of the implant stability measurements upon the length of the implant system. This study enables scientists to compare results of stability measurements for patients using different abutment lengths in the implant system.

Overall it is found that the implant system under study can be safely loaded with the hearing processor after one or two weeks on adults with normal expected bone quality. However, two weeks are advised to minimize possible soft tissue complications. The goal to obtain an inflammation free area of skin through better integration between implant and soft tissue has not yet been fulfilled and will still pose a challenge to future research and development. This will hopefully encourage scientist to pursue the development in implant design and operating technique.

DANSK RESUME

Implantatkirurgi til benforankrede høreapparater er et forholdsvist nyt område indenfor ørekirurgien. Implantation af en titaniumskrue i kraniet bag ved øret og fastgørelse af en vibrerende lydprocessor giver visse patienter med et konduktivt høretab mulighed for hørerehabilitering ved hjælp af benledning af lyden til det indre øre. Siden 1977, da den første implantation blev foretaget, har den kirurgiske teknik og implantatdesignet undergået en løbende udvikling med det fælles mål at opnå et fuldt osseointegreret implantat uden inflammation og infektion i den tilstødende hud. En vigtig faktor for at opnå en langvarig succesfuld implantation er tidspunktet for ibrugtagningen af lydprocessoren, idet tilstedeværelsen af lydprocessoren og patientens håndtering af denne kan forstyrre osseointegrationen og føre til inflammation i huden. Denne afhandling undersøger om en tidlig ibrugtagning svækker osseointegrationen og fører til øgede hudrelaterede komplikationer.

Afhandlingen er baseret på to kliniske studier og et laboratoriestudie. De kliniske studier udgøres af et randomiseret, klinisk forsøg og et prospektivt kohortestudie som er publiceret i 4 fagfællebedømte artikler i et højt anerkendte, internationalt tidsskrift. Laboratoriestudiet undersøgte bestemte egenskaber ved en af de målemetoder, der blev anvendt i de kliniske studier baseret på undersøgelser på tindingeben og gips.

Artikel 1 og 2 omhandler det randomiserede, kliniske forsøg. Artikel 1 omhandler den del af forsøget, der undersøgte stabiliteten og osseointegrationen af implantatet. Det blev vist, at en ophelingstid på 2 uger i stedet for de konsensusbaserede 4-6 uger var sikker i forhold til implantatstabilitet. Artikel 2 undersøger effekten på bløddelskomplikationer ved at undlade at foretage fjernelse af bløddelsvæv omkring implantatet, hvilket mentes at være essentielt for at nedbringe inflammationen omkring implantatet. Det blev vist, at komplikationsfrekvensen var mindre for den gruppe, der ikke havde fået foretaget bløddelsfjernelse.

Artikel 3 og 4 omhandler et studie af et nyt implantatdesign, hvor en overfladebelægning med hydroxyapatit er tilføjet den del af implantatet, der er i berøring med huden. Denne overfladebelægning tænktes at kunne nedbringe frekvensen af bløddelskomplikationer ved at foranledige en mere tæt kontakt mellem hud og implantat og derved forhindre bakteriel kolonisation i at opstå i grænsefladen. Ingen reduktion i komplikationsfrekvens blev fundet for dette implantatsystem, hvilket indikerer at der ikke er nogen positiv effekt fra overfladebelægningen. Dog kan dette resultat være påvirket af en negativ effekt af samtidig at tage implantatet i brug efter kun 1 uge, hvilket kan have overskygget en mulig positiv effekt fra overfladebehandlingen. Ibrugtagningen efter 1 uge blev fundet sikker i forhold til implantatstabiliteten.

Artikel 5 omhandler en detaljeret analyse af afhængigheden af stabilitetsmålingerne på længden af implantatsystemet. Dette arbejde gør forskere i stand til at sammenligne målingerne af stabiliteten for patienter med forskellig længde på implantatsystemet.

Overordnet blev det vist at det undersøgte implantatsystem kan ibrugtages efter 1 eller 2 uger hos voksne med forventet normal knoglekvalitet. Dog anbefales det at vente til 2 uger for at minimere hudkomplikationerne mest muligt. Målet om helt at kunne undgå inflammation i området omkring implantatet er endnu ikke opfyldt og vil fortsætte med at være en udfordring for fremtidig forskning og udvikling. Dette vil forhåbentlig anspore forskere til at fortsætte med at udvikle de kirurgiske metoder og implantatdesignet.

ACKNOWLEDGEMENTS

To Lars Vendelbo and Andreas Agger, my co-authors for much of the work leading to this thesis. You made it happen for me when I was still a novice in otology. Thanks for the mentoring and the fun skiing!

To Michael Gaihede, my supervisor for the thesis and close collaborator in otology. Your combination of scientific excellence, pragmatism and thoughtfulness will lay the foundation, I hope, for scientific collaboration and friendship in many years to come.

To Henrik Jacobsen, Head of the Department of Otolaryngology, Head and Neck Surgery, Aalborg University Hospital, for wholeheartedly supporting the completion of this project so that it could fit into my surgical career as an otologist.

To Bo, my best friend, in whose presence one feels more confident, fun, smart, competent, and executive. I guess we have discussed pretty much everything in our lives and every time we do, I grow a little bit. Thank you for the excellent time we spent together working on our PhD-theses in your summer cottage in beautiful Stockholm.

To my parents who taught me the art of self-discipline and meticulousness at the same time as showing by example that there is so much more to life than can ever be fulfilled by reaching an academic or professional goal.

To Finn Bojsen Møller, my anatomy professor at the start of medical school. Without knowing it he has been, and should be to others, an inspiration by expressing everything essential that could ever be said about teaching and learning: "…Det er min erfaring, at kundskaber og paratviden ikke står i vejen for overblik, vid, fantasi, menneskelighed eller faglig ydmyghed, som nutiden synes at mene. De er efter min bedste overbevisning netop forudsætningen herfor. Vi kan godt være selektive overfor den øgede mængde viden, men grundlæggende er der kun en måde at reagere på: at kunne noget mere. Nu er studenternes hjerne jo heller ikke en container, der skal beskyttes mod at løbe fuld, den er et bål, der skal antændes for at brænde ekspansivt og uudslukkeligt – og i den henseende er vi alle studenter, unge som gamle. Det er gentagelsen og brugen af det indlærte, der fører til perfektionen."

To Ina, Liv and Lea, my beloved wife and two amazing girls. If work hours sometimes seemed long, I made them feel shorter and brighter by imagining the time that could be released to be together with you by working more efficiently. Ina, the peace of mind you gave me by allowing me to focus on working on this thesis is invaluable, and the sacrifices that you have made can be considered an integrated part of this work.

LIST OF PAPERS

Paper 1

Høgsbro, M., Agger, A., & Johansen, L. V. (2015b). Successful loading of a bone-anchored hearing implant at two weeks after surgery: Randomized trial of two surgical methods and detailed stability measurements. *Otology and Neurotology*, *36*(2), e51-7. https://doi.org/10.1097/MAO.0000000000000647

Paper 2

Høgsbro, M., Agger, A., & Johansen, L. V. (2015a). Bone-anchored Hearing Implant Surgery : Randomized Trial of Dermatome Versus Linear Incision Without Soft Tissue Reduction - Clinical Measures. *Otology and Neurotology*, *36*(10), 805–811. https://doi.org/10.1097/MAO.0000000000000731

Paper 3

Høgsbro, M., Agger, A., & Johansen, L. V. (2017b). Successful loading of a bone-anchored hearing implant at 1 week after surgery. Otology and Neurotology, 38(2), 207–211. https://doi.org/10.1097/MAO.0000000000001312

Paper 4

Høgsbro, M., Agger, A., & Johansen, L. V. (2017a). Bone Anchored Hearing Implant Surgery: 1 Year Follow-Up Data Shows No Effect of Hydroxyapatite Coating on Soft Tissue Reaction After Loading at 1 Week. *Otology & Neurotology*, *38*(6), e152–e158. https://doi.org/10.1097/MAO.0000000000001442

Paper 5

Høgsbro, M., Gaihede, M., Agger, A., & Johansen, L. V. (2019). In vitro Investigation of the Dependency Between Abutment Length and Implant Stability Quotient (ISQ) for Stability Measurements on Bone Anchored Hearing Implant Systems. *In Preparation*.

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LIST OF ABBREVIATIONS

ASIST: Advanced System for Implant Stability Testing

AUC: Aarea under the curve

BAHA: Bone anchored hearing aid

BAHI: Bone anchored hearing implant

BAHS: Bone anchored hearing surgery

BIC: Bone-implant contact ratio

HA: Hydroxyapatite

IPS: Inflammation, Pain and Skin height

ISQ: Implant stability quotient

LI-NT: Linear incision, no thinning

LIT-r: Linear incision technique with reduction of soft tissue.

MIPS: Minimal Invasive Ponto Surgery

RTQ: Removal torque

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CHAPTER 1. INTRODUCTION

Patients suffering from hearing loss can be divided into two groups: those with a sensorineural or cochlear deficit, whose middle ear functions properly; and those with a conductive hearing loss, whose cochlea functions normally, but whose middle ear for some reason does not properly conduct the sound into the cochlea. Reasons for a conductive deficit include conditions such as atresia of the ear canal which can be either acquired or congenital; the status of the tympanic membrane; and the status of the middle ear including the functioning of the ossicles. The two types of hearing loss also coexist as a mixed hearing loss in which either of the two types may be dominant.

For patients with a pure sensorineural hearing loss, the first choice for rehabilitation is a conventional hearing aid that delivers amplified sound through the ear canal thereby stimulating the cochlea via the normal transmission route through the middle ear. If the hearing loss is more profound, this treatment may become insufficient, and it may be necessary to operate the patient with a cochlear implant. A cochlear implant stimulates the cochlear nerve fibers with small electrical signals thus bypassing both the middle ear and the sound wave propagation in the cochlea.

Patients with pure conductive or mixed hearing losses might also benefit from a conventional hearing aid which can be convenient and cost-effective; however, for some this is not a valuable solution. For example, patients with an atresia laterally in the external ear canal or microtia cannot use these conventional devices since the physical placement of the hearing aid may be impossible. Also, the ear canal or the middle ear may be draining due to medical or surgical complications which results in both a fluctuating hearing loss due to varying amounts of dampening fluids as well as obstruction and eventually malfunctioning of parts of the hearing aid that is placed in the ear canal. Further, the conductive component of the hearing loss may be so large that the hearing aid may have to be equipped with a closed plug in the ear canal which may cause complications such as discomfort, autophony, distortion, and cross stimulation of the other normally functioning cochlea.

For these patients, an alternative way of stimulating the cochlea exists by means of bone conduction which is the transmission of sound waves to the cochlea via the bone surrounding the middle ear and ear canal thus bypassing any middle ear deficiencies. Sound is obtained from a hearing processor that evaluates and amplifies the incoming sound signals and vibrates accordingly. The hearing aid is held in place by some stabilizing device (soft band, glasses, steel wire etc.) and can be placed at several locations, but the most used anatomical position is somewhere in the retroauricular area.

In 1969, it was discovered that titanium screws can be implanted in the maxilla and mandible to retain intraoral prostheses (P. I. Brånemark et al., 1969), and in 1977, this

technique was developed to also encompass implantation in the mastoid region (A. Tjellstrom, Lindstrom, Hallen, Albrektsson, & Brånemark, 1981). Since then, the preferable route of bone conduction has been via stimulation of a titanium implant in the mastoid region to which the hearing aid is attached. Most implants have a part that permanently penetrates the skin. In these cases the system is said to be percutaneous. The implant may also be covered by intact skin with the hearing aid acting through magnetic coupling in which case the stimulation is said to be transcutaneous; however, this solution requires an (almost) purely conductive hearing loss, which limits its use. If there is a substantial sensorineural hearing loss, there is too much damping by the skin for this solution to be feasible. Also, active implants have been developed in which the vibrator itself is implanted in the mastoid or coupled directly to e.g. the incus or the round window membrane in the middle ear. This thesis considers only the passive, percutaneous implants and surgical methods corresponding to these.

The discovery of the ability of the human body to sustain a long term integration of a titanium implant has revolutionized the field of bone conduction hearing. The possible sound levels that can be transmitted to the ear via a percutaneous implant are much greater than for the transcutaneous devices. This gives a much better hearing rehabilitation, and the percutaneous system also removes the symptoms of pain and discomfort from pressure onto the skin that were generated by the transcutaneous devices earlier in use. Of course, the system necessitates surgical intervention with some possible short and long term complications, so the benefits of better hearing rehabilitation must be weighed against these possible complications. The overall success of the implantation and later use of a percutaneous hearing implant relies on a complex combination of:

- The exact composition of the material, which must be biocompatible in order to assure osseointegration and soft tissue integration (or at least soft tissue acceptance).
- The implant design, which should allow for an easy and fast surgical procedure, give rise to mechanical properties that allow good sound transmission, and be optimized towards reducing soft tissue reactions in the skin surrounding the implant system.
- The surgical procedure, which should be optimized to enable a long term stable implant with a reaction free area of surrounding skin.
- Patient and environmental specific issues, which imply that the tissue of different patients may react differently to the implantation procedure and subsequent exposure to pathogens.

The research in this thesis should be seen in this context since it explores aspects of these complex relations. The overall aim of the work presented is to contribute to the optimization of the surgical implantation and post-implantation procedure through exploring if a certain development of implant design and material can work together

with a modification of the surgical procedure to create the possibility for earlier loading of the implant with the hearing processor than previously recommended.

1.1. BONE ANCHORED IMPLANT SYSTEMS

The bone anchored implant systems that are examined in this thesis are all percutaneous titanium implants made of commercially pure titanium (Figure 1). Although the implants are continually being developed and historically have undergone changes in design, material composition, and surface modifications, the basic structural design of the implant systems have essentially remained the same. The bone anchored hearing implants all have a screw-shaped implant part (as opposed to some dental implants that have other configurations, e.g. steps, fins or porosities (Brunski, 1999)) that is inserted into the bone after a specific drilling procedure. An abutment is attached to the implant with a screw to obtain a tight connection that will enable good sound conduction. The "hearing processor", which is an integrated sound processor and vibrator, is firmly attached to the abutment, typically with a snap connector making it easy for patients themselves to attach and detach the device as needed. Further relevant biomechanical properties of the implant system will be considered in more detail in later sections of the thesis.

Figure 1 *Example of a bone anchored hearing implant system.* ***A****: BI300 implant* ***B****: BA400 abutment* ***C****: sound processor BAHA 5. Published with permission from Cochlear Bone Anchored Solutions AB, Göteborg, Sweden.*

1.2. EVOLUTION OF THE SURGICAL METHODS FOR PERCUTANEOUS HEARING SYSTEMS

1.2.1. OVERVIEW OF THE EARLY IMPLANTATION TECHNIQUES

I 1981, the first report of a permanently skin-penetrating titanium implant to be used for the attachment of a vibrating hearing aid was published by the surgeons at Sahlgrenska University Hospital in Gothenburg, Sweden (A. Tjellstrom et al., 1981). At this time, it was known that titanium implants could be inserted into long bones and into the mandible or maxilla of man, but it was unknown whether the different embryologic origin and histologic appearance of the cranial bone in the mastoid area would cause any difficulties leading to implant loss. It was also known that a titanium implant could permanently penetrate the skin in the upper arm if the skin movement was restricted, but it was not known if the loading of a hearing aid onto the penetrating part of the abutment would lead to recurrent infections, eventually hampering the use of the hearing aid or leading to either a spontaneous loss of the implant or a forced surgical removal due to infection (A. Tjellstrom et al., 1981).

The surgical procedure originally proposed (A. Tjellstrom et al., 1981) is seen schematically in Figure 2. This method was a two-step procedure, both carried out under local anesthesia. First, the periosteum over the mastoid process was exposed through a linear or slightly curved incision, and the bone was subsequently exposed by raising a periosteal flap. Drilling was done just below the linea terminalis to the level of the dura, and the hole that was created was subsequently tapped, and a 3.75 mm wide, pure titanium fixture was inserted. The early abutments were only 4.5 mm in height since the implants were not deemed stable enough to support longer abutments that would exert a larger destabilizing torque on the implant (Verheij, Bezdjian, Grolman, & Thomeer, 2016). The incision was sutured, and 3 to 4 months later, the second step of the procedure was carried out. Under local anesthesia, a hole was punctured over the titanium fixture, and the abutment for attachment of the hearing aid was screwed onto the fixture. No soft tissue reduction was carried out for the first patients, and the abutment was long enough to stick out only 1-2 mm above the level of the skin. These first patients comprised both patients who used their implant for attachment of a hearing aid and patients who used the implant for the attachment of an auricular prosthesis. The implants were the same, but could of course be influenced differently due to e.g. moisture accumulation beneath a prosthesis. Although implants are also still used today for attachment of prosthetic devices, later reports divide the patients according to the use of the implants.

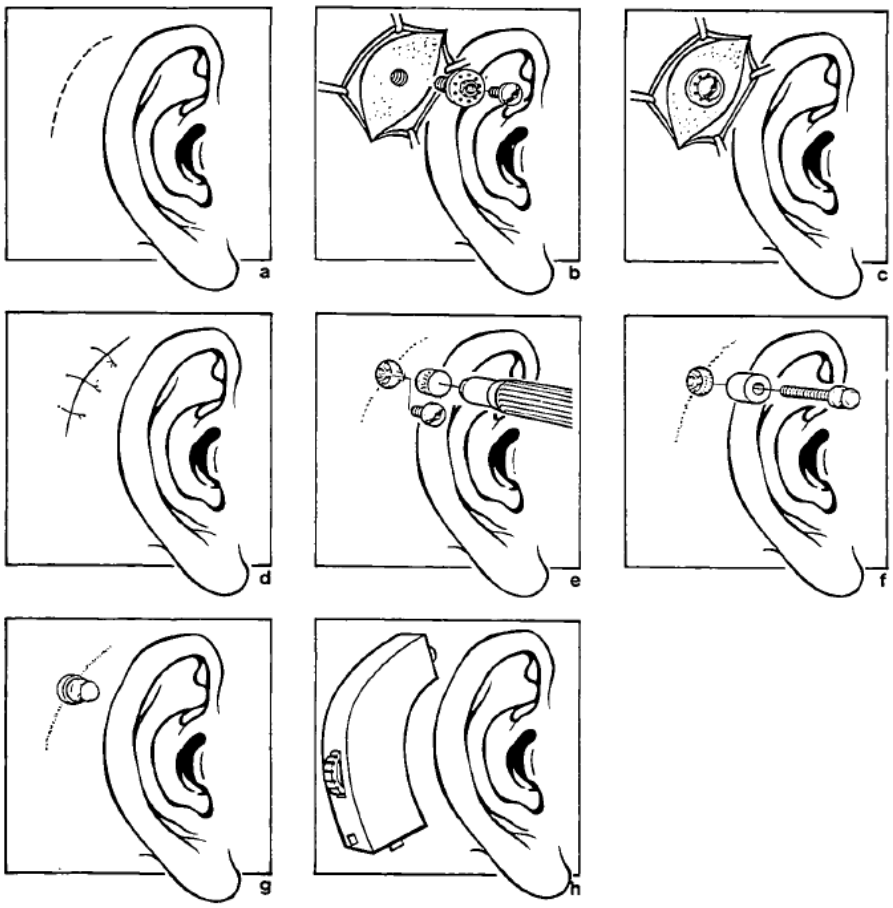

Figure 2 *Schematic drawing, representing the surgical procedure proposed in the first report of a permanently skin penetrating titanium implant* (A. Tjellstrom et al., 1981)

In the beginning, only a very limited reduction of the soft tissue was performed during the first step of the procedure. It was noted that some of the patients with thick soft tissue layers would have inflammation and superficial infection around the abutment which would disappear after the reduction of the soft tissue around the implant. Therefore the technique was modified to incorporate soft tissue reduction in the first step of the procedure (Tjellström, Lindström, Hallén, Albrektsson, & Brånemark, 1983). This was also in accordance with an analysis of the interface zone between implant and tissue (Albrektsson et al., 1983) proposing that limiting the movement between abutment and soft tissue would lead to a more undisturbed interface that would allow for a more tight connection between abutment and soft tissue.

In a report of the first five years experience with these first patients, the surgical method is modified to postpone the reduction of the soft tissue to the second step, carried out no earlier than 3 months after implantation. If the implant was situated in a region with hair follicles, a pedicled or free skin graft without hair follicles was used to cover an area of no less than 7 mm around the abutment (Tjellström, Rosenhall, et al., 1983). In a later report of the first patients operated on between 1977 and 1985 in Gothenburg, it is stressed that in order to minimize skin reactions around the percutaneous implant, a close contact between skin and bone (periosteum) is sought for, and the subcutaneous tissue is accordingly reduced in an area of around 10 mm around the implant during the second step of the procedure. A healing cap would be placed to enable ointment soaked gauze to be placed around the abutment, and this would be changed every 4 days for two weeks. Then the hearing aid would be loaded on the abutment after another week necessitating 4 visits to the out-patient clinic. A success rate for the skin status of 97.5% based on the total number of observations of the Holgers 0-1 grades (see description in section 1.4.2) was reported. The failure rate for extrusion of implants was calculated to 0.2% per observational month based on three implant losses during a total follow-up time of 1515 months. (Holgers et al., 1988).

The skin's ability to accept a permanently penetrating titanium implant was further examined in another early report, where a rate of Holgers grade 0 in 87.5% of 36 patients was found. In this study, the importance of reducing the soft tissue was stressed although this was not supported with any kind of comparison (Portmann, Boudard, & Herman, 1997). The success rate in this study was somewhat lower than for the studies by Tjellström et al. (87.5 % vs. 93.3% for Holgers score 0), and this difference was partly ascribed the shorter duration of experience and that the skin graft surrounding the abutment might not have been thin enough. This is not based on references to clinical comparisons but rather to statements from Prof. A. Tjellström.

In the early era of research on percutaneous implants in the mastoid region, it was a strong belief that reduction of soft tissue to the level of the periost or even also removal of the periost (Mylanus & Cremers, 1994) was the key to success in that it allowed for a stress-free interface between the percutaneous implant and the surrounding skin (graft) (Tjellström, 1985). It was hypothesized that it would be of value if tissue lipids and proteins could form a strong chemical bond between the skin and implant. Furthermore, it was pointed out that the surface of a titanium implant is not metallic titanium but rather titanium dioxide, TiO_2, and that every handling of the titanium implant from machining and sterilizing to perioperative handling could influence on the exact composition of this surface, and hence influence the osseointegration of the implant and acceptance of the abutment at skin level (Tjellström, 1985).

Although the early success rates seem quite convincing for the method to be considered a success, it was estimated that the method could be further developed in order to minimize the surgical complications and that too many patients suffered from

recurrent periods of inflammation or more severe infections around the implants (Stalfors & Tjellstrom, 2008). To this end, two modifications of the procedure was introduced for the management of the soft tissue around the implant, namely the U-graft technique (illustrated in Figure 3) and the dermatome technique (illustrated in Figure 4). With the U-graft technique, the goal was to obtain a hair free area around the implant in the closest possible contact with the underlying periosteum in order to reduce inflammation and thickening of the skin with eventual overgrowth of epidermis on the abutment. The U-graft technique was a development of another (unnamed) method in which the skin at and around the implant site was totally excised together with the subcutaneous tissue and covered with a hair free transplant from the retroauricular fold. This method was abandoned due to complications with partial graft necrosis, which was observed in 16% (Stalfors & Tjellstrom, 2008). With the U-graft technique, a U-shaped incision is performed around the implant site and the graft is mobilized down to the level of the periosteum. All soft tissue is removed and care is taken to remove all hair follicles from the dermal graft since remaining hair follicle or remnants thereof were hypothesized to be the origin of foreign body reactions, and hence inflammation. The incision is undermined in order to obtain a smooth and gradual transition to the implant area. Incision of the periosteum, drilling, and insertion of the implant remained unchanged (until the introduction of a self-tapping implant in 2001) (Stalfors & Tjellstrom, 2008).

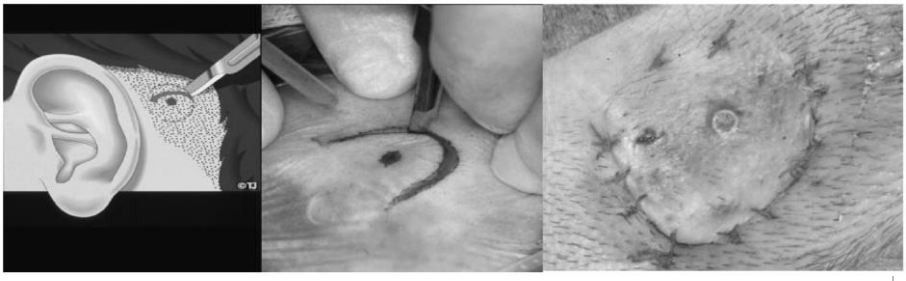

Figure 3 *Illustration of the U-graft technique* (Stalfors & Tjellstrom, 2008)

The goal of the dermatome technique was essentially the same, namely that a thin layer of skin, free of hair follicles, must surround the abutment and be in close contact with an intact layer of periosteum. The dermatome that was specifically developed to this surgical procedure slits a skin graft 25 mm wide and 0.6 mm thick. The skin graft was harvested at the implant site and could either be left with one side attached where the harvesting ends, or it could be cut totally from the adjacent skin. Soft tissue reduction is done by totally removing all subcutaneous tissue under the skin graft and also by undermining the skin to obtain a smooth transition to the periosteum bed. The elevated skin graft was subsequently punched with a hole to allow for the placement of the percutaneous abutment through the skin and sutured to the intact skin edges.

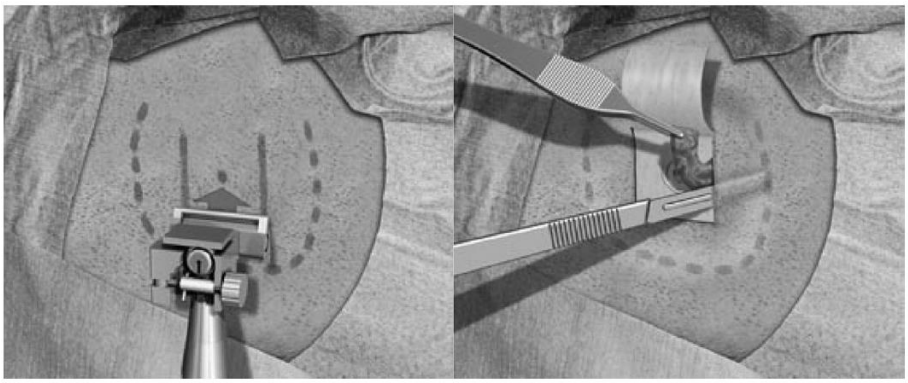

Figure 4 *Illustration of the dermatome technique* (Stalfors & Tjellstrom, 2008)

Simultaneously with the development of the grafting part of the surgical procedure, modifications were done with regard to staging. Due to the good results concerning long-term stability, a one-stage technique was introduced by the team in Göteborg in 1989 and reports from 1993 and 1994 show how other centers adopted the procedure with slight modifications (Mylanus & Cremers, 1994; Proops, 1996). The difference between the one-stage and two-stage procedures is that in the one-stage procedure, after soft tissue has been reduced and the implant site has been covered with some kind of graft (differing between centers), the graft is immediately punched with a hole and the abutment fastened to the implant through this hole. Thus, in the healing period in which the free skin graft will need to re-establish its vascularization it is now also burdened with the surgical trauma from punching the hole for the abutment and from the subsequent piercing of the abutment.

The technique presented in 1994 (study beginning in 1991) that incorporates the single stage technique also introduces a linear rather than a curved incision, since this leads to easier access to soft tissue reduction all around the implant and no partial or total graft necrosis (Mylanus & Cremers, 1994). Skin is still removed in a circular area around the implant together with the soft tissue, even including the periosteum. A hair-free skin graft from the retroauricular area is used to cover the defect. With this method results were comparable to the two stage technique concerning implant survival rate and soft tissue issues. A variation of this technique uses 4 supplementary radial incisions to ease the soft tissue reduction with direct visual control (Narayana Reddy, Dutt, & Gangopadhyay, 2000).

Another report underlines the importance of reducing the soft tissue in the surgical procedure (Proops, 1996). Here, it is advocated to radically remove all soft tissue down to the periosteum in a circular area with diameter of 4 cm around the implant and most importantly to reduce some of the temporalis muscle to avoid an eventual prolapse of the muscle tissue on the top of the abutment. Initially a two-stage procedure was used but eventually converted to the simpler one-stage procedure for

almost all adult patients. These authors make use of a free split skin graft elevated by using a 'Silver's' dermatome. The failure rate for loss of implants is 10.1% (19/188, follow-up period not specified), but these numbers include some patients that were fitted with both a hearing aid and an auricular prosthesis. No data for soft tissue reactions are reported.

Other surgical procedures for grafting the implant area have been published. A circular split skin graft 3 cm in diameter centered on the implant site was elevated, preferably with a scalpel 10 blade, and used to cover the area around the abutment. This technique was used in 25 patients from 1993 to 1999 (Woolford, Morris, Saeed, & Rothera, 1999). Care was taken to remove all hair follicles and the surrounding skin was undermined and soft tissue was reduced. No implants were lost during one year of follow-up, and in 16% significant early skin graft inflammation was noticed. At another surgical center, a Z-transposition flap of post-auricular skin was used (G G Browning, 1990; George G Browning & Gatehouse, 1994).

One conceptual change in the management of the soft tissue surrounding the abutment was introduced around 1997 as the linear incision technique with soft tissue reduction (LIT-r) but without removal of surrounding skin, thereby omitting the need for a skin graft (De Wolf, Hol, Huygen, Mylanus, & Cremers, 2008). With this technique, a linear incision of approximately 3 cm is made centered on the planned implant site, 50-55mm posterosuperiorly to the external ear canal. Soft tissue is removed in an area of about 2 cm under the skin flap to both sides of the incision and the skin is thinned manually with a scalpel blade by excision and scraping the remnants of hair follicles. Periosteum in the exposed field is also removed with the aim of providing a hair less skin site that can attach itself to the bony layer. The abutment is placed either through a hole, punched in the skin or in the incision line as is deemed most appropriate during the procedure. This modification of the procedure represents a major simplification since no graft (or flap) was used. No necrosis was observed, the surgical time decreased and the donor site morbidity sometimes observed with the skin graft techniques was eliminated. Results from this procedure with a mean follow-up time of 5,6 ± 2.7 years were comparable with other studies using the same implants with a total extrusion rate of 9.3%, with 3,3% related to surgical issues (infection, skin overgrowth or pain) and an observation of Holgers grade 2 or more in 6,5% of the 1038 follow-up visits (De Wolf et al., 2008). Implants were loaded after 6 to 8 weeks to ensure adequate osseointegration and the patients were treated with antibiotic ointment for three weeks, the first week using a slightly compressing gauze and the last two weeks from a daily application around the abutment. A variation of this technique uses a cruciate incision but is otherwise essentially the same (Persaud, Papadimitriou, Siva, Kothari, & Quinn, 2006).

In summary, in the early 2000s, surgical procedures could be broadly divided into two groups. The first group consisted of the linear incision with the reduction of soft tissue and the second group consisted of a mixture of various techniques, all making use of

soft tissue reduction and some kind of skin graft to cover the excised skin using various techniques (Berg, Stokroos, Hof, & Chenault, 2010).

In 2005 a consensus statement on the bone anchored hearing aid implant system was published following round-table discussions by experts in the field (Snik et al., 2005). The aspects of the surgical procedure that were evaluated led to the consensus that for adults, the one stage procedure could be used and implants should be loaded no earlier than after 4-6 weeks to ensure lasting osseointegration. In children up to the age of about 10 years, the two stage procedure was still acknowledged to be safer and the implants should not be loaded before 2 weeks after the second step when soft tissues were adequately healed. For all patients, in order to avoid skin reactions after surgery, reduction of soft tissue was deemed very important.

1.2.2. THE LINEAR INCISION WITHOUT SOFT TISSUE REDUCTION

Since its introduction in 1977, the implant and abutment had not changed substantially. But in 2010 a new system with longer abutments (the BA300's) were introduced, so that now the surgeon could choose between abutment lengths of 6 and 9 mm. To support these longer abutments that would generate a larger torque on the implant-bone interface, a new, wider implant was introduced (the BI300, Cochlear Bone Anchored Solutions, Mölnlycke, Sweden). This implant is 4.5 mm in diameter, and therefore intrinsically more stable prior to proper osseointegration than the immediate predecessor implant that were 3.75 mm wide (BAHA flange fixture, Cochlear Bone Anchored Solutions, Mölnlycke, Sweden). The BA300 abutment has an "as machined" titanium surface, which in this context means that the titanium surface is not modified in any way after production, leaving only small irregularities on the surface. At the time, there was a wish to optimize the surgical procedure to reduce the rate and degree of soft tissue inflammation and to obtain better cosmetic outcomes (M Hultcrantz, 2011). Thus, it was proposed that a new operating technique in which no soft tissue nor hair follicles are removed would be feasible with the wider implants and longer abutments. A prospective study of these first patients reported good outcomes with only 1 out of 7 patients having a Holgers score of 2 within 12 months of follow-up. Furthermore, none of the patients had epithelial overgrowth (M Hultcrantz, 2011) and no implants were lost. The surgical procedure involved the same steps, just without soft tissue removal, as the linear incision with soft tissue reduction and is more thoroughly described in paper 1 and 2.

1.2.3. LOADING TIMES

As to the recommendation from the consensus statement a healing period of 4-6 weeks was used at this time, to make sure that the implant would be osseointegrated before loaded with the hearing processor (Snik et al., 2005). However, some surgeons at the time were tweaking this, e.g. in a study where loading after one step surgery usually

would be by the end of the third week for 25 patients from 1993-1999 (Woolford et al., 1999).

With the 2010 introduction of the BIA300 implant system, surgeons believed that earlier loading times could be feasible owing to the greater intrinsic stability of the implant and several studies investigated the possibility of reducing the loading time towards two weeks with great success since survival rates of 96-100% were reported for studies on adult patients (Wigren, 2016). Thus, at the time it was a natural next step to pursue the possibility of further shortening the loading time. This was also encouraged by the development in dental implantation where immediate loading had been feasible since the 1990's (Daniel Buser, Sennerby, & De Bruyn, 2017). However, it should be remembered that dental implants are much longer than hearing implants (6 mm - 14 mm vs. 4mm) and therefore much more intrinsically stable in accordance with the much more pronounced mechanical loading forces they should withstand. However, even though these results from dental implants can in no way be expected to carry over directly to hearing implants, at least the proof of concept existed that an implant can become successfully osseointegrated even if it is loaded during the osseointegration phase if it is mechanically stable enough. This fact was naturally inspiring otologists to pursue earlier loading.

1.3. TISSUE INTEGRATION OF TITANIUM IMPLANTS

1.3.1. OSSEOINTEGRATION

Implantation of titanium implants into the human body has been the subject for quite intense research since Brånemark in the 1960s and 1970s started experimenting with this metal (Albrektsson et al., 1983). Through a series of laboratory, animal and human in-vivo studies, it was discovered that human bone could live in close contact with the metal surface with the osteocytes making biological contacts with the surface, as could be visualized by electron microscopy (Albrektsson et al., 1983; Branemark, 1983). This integration of inorganic material into human bone was termed osseointegration and can be defined as "continuing structural and functional coexistence, possibly in a symbiotic manner, between differentiated, adequately remodeled, biologic tissues and strictly defined and controlled synthetic components, providing lasting, specific clinical functions without initiating rejection mechanisms" (R. Brånemark, Brånemark, Rydevik, & Myers, 2001).

Most of the early work on osseointegration was done with dental implants so a lot of the basic scientific knowledge in bone anchored hearing implants rely on insights from this field. Dental implants and bone anchored hearing implants (BAHIs) shares a lot of common factors, but one must always be aware of the differences that exist between e.g. implant design (longer dental implants), bone morphology (maxilla and mandibula versus temporal bone), local conditions (mouth versus skin), loading stress (much higher for dental application) when comparing results.

To ensure long term osseointegration, it is of paramount concern that corrosion of the implant does not take place to any significant degree. It has been shown, that titanium exhibits a very useful feature to this end, since a very stable layer of titanium oxide forms on the surface of the implant resulting in the observed inertness of the implant towards the implantation site (A. Tjellstrom et al., 1981). This layer essentially protects the metallic titanium in the middle of the implant from further corrosion. For this reason, titanium has gained widespread use for dental and orthopedic use and is the only material in use for BAHIs. Work in dental implantation on other materials, e.g. zirconium dioxide is ongoing (Daniel Buser et al., 2017).

When implanting a titanium screw into scull bone, a hole should be drilled to be able to fit the implant. The implants that are used today are all self-tapping, but the earliest implants needed tapping, which was done with a specialized titanium tap. It is customary to use drills with a diameter that is optimized for the implant, and for the implant under study in this thesis drills with a width of 4.1mm are used for the implant with an outer diameter, counting the threads of 4,5 mm (Lars Sennerby, Gottlow, Rosengren, & Flynn, 2010). Using an undersized drill by as little as 0,3 mm can enhance primary stability but also results in major bone remodeling (Stocchero et al., 2018). It is important not to drill with too high speed and to use abundant saline irrigation, in order to keep the temperature of the remaining osteocytes low (Eriksson & Albrektsson, 1984). The drilling procedure proposed by the manufacturing company uses two drills: a guide drill and a widening drill that also makes a countersink of 0,5mm to level out the bone for the flange of the implant (Key dimensions and material information for BI300 Implants & BA400 Abutments, Cochlear Bone Anchored Solutions AB, Göteborg, Sweden).

The insertion torque should be adapted so as not to damage the bone by squeezing. It is estimated that bone in the vicinity of 1mm from the implant is affected by the insertion and will undergo subsequent remodeling despite optimal surgical technique (Brunski, 1999).

The inserted implant will have some initial mechanical stability that is influenced by its length, width, tapping configuration and the quality of the surrounding bone. When the process of osseointegration begins and if it is successful, new bone will be formed by the process of intramembranous bone formation into close contact with the implant surface. Intramembranous bone formation proceeds in well-described steps including blood clot formation, angiogenesis, invasion of osteoprogenitor cells, formation and compaction of woven bone and lastly, after about 6 months, secondary bone remodeling (Brunski, 1999).

It is controversial whether the process of bone formation is controlled only by internal factors trying to heal the bone in the best possible way or whether the implant triggers an immunologic reaction to guide the formation of bone (Albrektsson, Chrcanovic, Mölne, & Wennerberg, 2018; Bielemann, Marcello-Machado, Del Bel Cury, & Faot,

2018). In rabbits this process of bone healing around the implant involves the activation of the immune system that tries to isolate the implant from the bone marrow by forming new cortical-like bone at the interface (Trindade et al., 2018).

In some cases, the process of osseointegration is disturbed and instead of bone formation, a layer of fibrous tissue can form in the implant-bone interface leading to a less stable implant with an increased risk of eventual rejection or loss due to small disrupting forces. It is believed that excessive micro motion in the early healing phase is the single most important factor for this kind of failure (Brunski, 1999). The fibrous tissue formation is thought to occur because excessive micro motion will interfere with the tissue repair process and vascular structure regeneration that take place in early bone healing. This will in turn provoke repair by collagenous scar tissue instead of bone formation (Brunski, 1999). It is estimated that micro motion of about 100 µm is enough to start this process (Szmukler-Moncler, Salama, Reingewirtz, & Dubruille, 1998). It is believed that high initial stability and consequently small micro motion is a prerequisite to successful osseointegration and is more important than the timing of loading the implant (Östman, 2008). If the implant is initially stable enough, no micro motion will take place, and the implant will eventually be osseointegrated.

It has also been postulated that the process of osseointegration can be influenced negatively by the inflammation process that takes place in the skin around the abutment. This inflammation process might lead to epithelial downgrowth on the implant-bone contact leading to disturbance in osseointegration (Abdallah, Badran, Ciobanu, Hamdan, & Tamimi, 2017; Larsson et al., 2015). Since the inflammation process taking place in the soft tissue is obviously dependent on whether or not soft tissue reduction has taken place, there is also a possible, indirect influence on the osseointegration process depending on whether or not soft tissue has been reduced.

In dentistry, during the 1990s immediate loading protocols emerged due to changes in the implant surface (Daniel Buser et al., 2017). Implants with a moderately rough surface prepared with a high grit sand blasting and acid-etching technique showed higher initial stability and better bone apposition than other surfaces (D Buser et al., 1991).

Good initial stability will ensure that micro motion is limited to levels below a damaging threshold, and it is therefore a prerequisite for early loading of an implant. Initial stability is influenced by the geometry of the implant since an increasing diameter will result in more rotational resistance and tapering of the implant will give more lateral stability due to compression, and adding small threads just below the flange can slightly compress the superficial bone also stabilizing the implant (Ivanoff, Sennerby, Johansson, Rangert, & Lekholm, 1997).

The BI300 implant, which was used in paper 1-4 in this thesis, has a surface that is prepared in the same way as the dentistry implants used for immediate loading - the

TiOblast surface (Astra Tech, Mölndal, Sweden). As mentioned, the implant is also wider than the previous implant with a diameter of 4.5mm. Since the width of the implant is important for mechanical stability, it was assumed that this implant would have a higher initial stability than the former implant.

The implant was tested pre-clinically in an animal model using 60 BI300 implants and 60 BA210 implants in rabbit tibiae. The implant was initially more stable and showed higher stability at all time points from 5 to 28 days. With the assumption that rabbits are approximately 3 times faster in bone healing than man this indicated that the BI300 implant would be as stable after two weeks as the old implant was after 3 months (Lars Sennerby et al., 2010). There is evidence that the osseointegration due to the rougher surface progresses with a process called contact osteogenesis where bone is directly formed on the implant surface compared to the less efficient process of distance osteogenesis where bone is formed only from the remaining bone surface and progresses into the tapping configuration of the implant (Lars Sennerby et al., 2010). This is thought to be due to differences in how the initial blood clot that is formed in the interface after implantation shrinks during absorption. Along the smooth surface the blood clot will shrink uniformly and leave a gap between bone and implant whereas with the more rough surface, the blood clot will shrink but not detach completely from the surface, allowing primitive cells to migrate closer to the implant before starting bone formation (Lars Sennerby et al., 2010).

Peak insertion torque is a common way to assess initial stability. If it is possible to insert the implant with a high torque before it starts to rotate in the implant bed, it will have higher initial stability. For the pre-clinical testing in rabbit tibiae, an insertion torque of 30Ncm was used (Lars Sennerby et al., 2010). Insertion torques of 40-50 Ncm are recommended for the bone anchored hearing implants in man (Surgery guide, Cochlear Bone Anchored Solutions, Göteborg, Sweden).

At the time of the study design it was not known whether loading the implant during this potentially vulnerable period, where osseointegration begins to form, would lead to a disturbance of the osseointegration process resulting in implant losses; however, based on the above mentioned experimental studies and clinical studies mentioned in paper 1 and 2 and (Wigren, 2016) it was hypothesized that the implant would be stable enough to support early loading.

1.3.2. SOFT TISSUE INTEGRATION

Although permanent osseointegration is a prerequisite for the overall success of a bone anchored hearing aid, also the interaction between soft tissue and titanium is important for the overall success of the implant-abutment system, since these implants permanently penetrate the skin. Problems with inflammation are common at the penetration site, although usually they consist of local inflammation that tends not to progress to more elaborate morbidity. Analogies for the penetration zone around a

percutaneous implant have been made to naturally occurring penetrations from teeth and nails, antlers, horns, hooves, feathers and tusks, and examinations of the connections around these types of tissue have been carried out in the hope of finding a way to artificially engineer the interface between implant and skin to be as trouble-free as these naturally occurring penetration zones (Abdallah et al., 2017). Interestingly, most of these seemingly penetrating structures are actually not skin-penetrating (horns, hooves, hair, fingernails, and feathers), since they are derived from epidermal invaginations and therefore do not breach the epithelial barrier. Teeth, deer antlers and babyrusa tusks are probably the only examples of true penetrating structures where nature has developed special designs to overcome the problems also relevant to a percutaneous device. Of these, the babyrusa tusks are most relevant to the study of percutaneous implants, since the babyrusa tusks are actually teeth from the maxilla that grow out through the skin instead of through the mucosa of the mouth. The study of these structures have led to insights into the cellular and molecular structures that are responsible for the tight connections at these penetration zones and these trouble free naturally occurring penetrating devices constitute the gold standard for the integration of a manufactured percutaneous device (Abdallah et al., 2017).

The problems that arise in the skin-abutment interface are meant to be related to lack of a tight connection and it is thought that making the skin adhere tightly to the surface of the abutment can eliminate most of these problems (van Hoof et al., 2015). Epithelial downgrowth (also named marsupialization) may develop as an apical migration of epithelial cells along the abutment surface, probably because the skin is in a permanent state of healing, trying to close the gap between its edges. Colonization with biofilm may arise, giving rise to an (intermittent) immune response, inflammation, swelling and pain and can result in more serious infection or abscess formation. Lately, a study on the cytokine expression profile in the peri-implant tissue 12 weeks after implant surgery revealed up-regulation of genes belonging to inflammatory cytokines, anabolic and tissue-remodeling proteins, signifying an ongoing remodeling process (Calon, van Tongeren, Omar, Johansson, & Stokroos, 2018). One recent study found that a hyper-polished surface could not reduce bacterial colonization or clinical outcome during one year follow-up. Furthermore, the study found anaerobic bacteria in the soft tissue in the vicinity of the implant both at time of implantation and at follow-up, indicating that a possible route of bacterial colonization is via the soft tissue and not only from contamination from the skin to the implant surface (Trobos et al., 2018).

Evidence that the length of the abutment itself can have an influence on the amount of inflammation, or at least its importance for creating clinical problems, was found in a retrospective report of 39 cases with intervention due to inflammation or skin overgrowth/thickening. Here, a reduction of Holgers grade after the abutment was changed to a longer 8.5mm abutment was found (Dun, Hol, Mylanus, & Cremers, 2011).

Another proposed solution is to find a more biocompatible surface coating, and work has been done with different materials; however, to date there has not been any demonstration of a strong integration in the soft tissue-device interface for any of the materials (Abdallah et al., 2017). However, at the time of the initiation of the work for this thesis (study 3 & 4), an abutment covered with hydroxyapatite (HA) had just been introduced (Figure 5). Its development was based on basic research with other percutaneous devices on e.g. dogs where a dense hydroxyapatite coating showed good skin integration whereas a porous HA-coating lead to serious infection after 1 month (Shin & Akao, 1997). A retrospective case study of 6 patients with 16 custom made percutaneous implants for craniofacial reconstruction with a hydroxyapatite coated subcutaneous flange, but otherwise diamond like coating in the percutaneous part, showed likewise signs of strong adherence between skin and implant (Kang, Morritt, Pendegrass, & Blunn, 2013).

Figure 5 *Implant and abutment system, with hydroxyapatite coating on the part of the abutment intended for skin contact. Implant: BI300, Abutment: BA400. Pictures © Cochlear Bone Anchored Solutions AB, Göteborg, Sweden.*

Initial reports from animal studies with the BA400 implant showed promising regarding the nature of the abutment-skin interface. It was shown that epithelial downgrowth and pocket formation were more restricted for HA-coated abutments than for pure titanium after implantation for 4 weeks in sheep and healthy tissue was found in close connection with the abutment (Larsson et al., 2012, 2015). These studies also point to the possibility that implant curvature can influence the interface in that the differences were more marked for a concave shaped abutment.

Even though the BA400 abutment was CE-marked in June 2012, no reports about the implant system from clinical studies or case series were available at the time of designing the studies for this thesis. Those of the above findings that were present at the time of study design were suggestive that the hydroxyapatite-coated abutment would lead to less peri-implant inflammation in the clinical setting.

1.4. METHODS

1.4.1. IMPLANT STABILITY QUOTIENT MEASUREMENTS

Quantitative evaluation of the stability of a bone implant is not easily done. First, the question arises about what is meant with "stability". An implant might be stable towards forces working in one direction (e.g. outwards), while unstable towards forces working in another direction (e.g. sideward/laterally or rotationally). Of course, what is important from a clinical viewpoint is stability towards forces that arise in a clinical context and these are mostly sideward from the gravity and the handling of the hearing processor. A direct approach that can be used in animal models for research purposes is to simply unscrew the implant while at the same time measuring the removal torque (RTQ) (Lars Sennerby et al., 2010). This measure is correlated to the bone-implant contact ratio (BIC); hence, it gives a good view of the level of osseointegration (Ivanoff, Sennerby, & Lekholm, 1996; Lars Sennerby et al., 2010). Unfortunately, this destroys or at least disturbs the osseointegration, which is not guaranteed to fully reestablish, and due to the purely rotational force applied, it might not be the most clinically relevant measure (Lars Sennerby & Meredith, 2008). A modified removal torque assessment can be applied with the application of a reduced torque that osseointegrated implants would resist. Implants that rotate under this torque could be considered as failures and removed. This test, however, is debated since implants considered failures with this test have shown to osseointegrate later, and since the method might cause small fractures in the bone around the osseointegrated implants, possibly leading to eventual failure for implants that were deemed osseointegrated by the test (Lars Sennerby & Meredith, 2008).

The first non-invasive method to be developed was the "Periotest" which was used primarily to measure stability of living teeth by measuring the damping characteristics of the periodontium (Schulte & Lukas, 1992), but has not found widespread use in implantology, since it could not cover the higher stiffness of the osseointegrated implant (Atsumi, Park, & Wang, 2007; L Westover, Faulkner, Hodgetts, & Raboud, 2018). Recently, a development of this measurement technique, the "ASIST (Advanced System for Implant Stability Testing)" has been published (L Westover et al., 2018). It relies on measuring the acceleration of a small impact rod while it shortly impacts on the abutment. By analyzing the impact acceleration signal using an analytic model where the length of the abutment and other component characteristics are parameters it is possible to obtain a normalized measure of the bone-implant stiffness that is not dependent on the component characteristics, most notably the abutment length (L Westover et al., 2018). The measurement method is more sensitive than the Implant Stability Quotient (ISQ, see next paragraph) for detecting differences in stability (Lindsey Westover, Faulkner, Hodgetts, & Raboud, 2018) and was recently used in a clinical setting but is not (yet) commercially available (Lindsey Westover, Faulkner, Hodgetts, Kamal, et al., 2018).

The method used in this thesis is the Implant Stability Quotient (ISQ) measurement (Osstell AB, Göteborg, Sweden), which is essentially a measure of the lateral stability of the implant (Lars Sennerby & Meredith, 2008). It takes advantage of the fact that the bone-implant connection will never be completely rigid, since the elastic properties of bone will allow for small movements of the implant when subjected to a lateral force. From basic physical principles it is known that the application of such a lateral force will set the implant into vibration, and that the system will have characteristic frequencies at which vibrational amplitude is at an optimum, so-called resonance frequencies. These resonance frequencies are dependent on the total elastic properties of the system in such a way that if there is a tighter connection between the implant and bone, the stiffness of the system will increase and the resonance frequency will be higher, and if the stiffness of the system is lowered, e.g. by loosening of the implant, the resonance frequency will decrease (Lars Sennerby & Meredith, 2008). Of course, all factors defining the total stiffness of the system might influence on the ISQ, so, theoretically, the ISQ is not a measurement of the degree of osseointegration. However, if all other factors other than bone-implant contact are held constant, a change over time in ISQ will reflect a change in osseointegration, and therefore the ISQ is clinically relevant.

Figure 6 *Example of Implant Stability Quotient measurement with the Osstell ISQ.*

In the actual implementation of the measurement system, it is not the resonance frequency of the implant, but rather the resonance frequency of a transducer attached to the implant or abutment that is measured. The resonance frequency of the

transducer will depend on the total stiffness of the vibrating system, and thereby on the stiffness on the implant-bone interface.

When first developed, the ISQ measurement system was a wired measurement of the resonance frequency of a transducer attached to the implant. A major drawback was that this transducer had its own resonance frequency that would have to be calibrated before actual measurement. However, the basic principle was useful, and the measurement system was developed into the latest commercially available device, the "Osstell ISQ" (Osstell AB, Göteborg, Sweden) (Lars Sennerby & Meredith, 2008). This apparatus is handheld and wireless. The transducer is a small rod with a magnet at its end (a "SmartPeg", (Osstell AB, Göteborg, Sweden)). The SmartPeg is attached to the implant or the abutment via the use of the center screw with a torque of approximately 5 Ncm. A stimulating magnet in the end of the handpiece is controlled automatically by the handheld device. When this magnet is brought into the vicinity of, but not in contact with, the magnet on the SmartPeg, the apparatus senses the vicinity of the magnet and starts to make stimulating impulses between 1 and 10 kHz, essentially setting the SmartPeg into very small vibrations. Stimulation is done in two perpendicular directions in a plane perpendicular to the SmartPeg, so that the peg is effectively set into rotational motion. A sensor in the tip senses the resulting electromagnetic radiation and compares this with the stimulating signal. From this, the resonance frequency can be calculated. For convenience, the resonance frequency is converted to a number on the ISQ-scale which goes from 1 to 100 (Lars Sennerby & Meredith, 2008).

Because of the rotational excitation pattern, the resonance frequency can be evaluated for all different directions in the plane of excitation at once and the apparatus measures the highest and lowest values for this resonance frequency, if they differ by some preset amount (3 ISQ) (H. Johansson, Jonasson, & Johansson, 2015). This is useful especially if evaluating dental implants that are placed in the highly inhomogeneous bony surroundings of the maxilla and mandible, whereas in the temporal bone, the resonance frequency will usually be more homogenous.

Importantly, the stiffness of the system, and hence the ISQ measure, is dependent on the total length of the system. This length is composed of the length of the SmartPeg, which is fixed, the length of the abutment, which can vary in fixed intervals, and the length of the implant above the bone surface, which is fixed if the implant is fully inserted (Lars Sennerby & Meredith, 2008). If the abutment is longer, the stiffness of the system, and hence the ISQ-measure, decreases. Therefore, to compare ISQ measurements for different abutment lengths, they have to be converted to some common reference, most appropriately the ISQ that would have been obtained without the abutment, i.e. with the SmartPeg attached directly to the implant. Unfortunately, at the time of investigations for this thesis, no such information was published and in order to compare measurements between patients we had to rely on personal

communications with the manufacturer. This relationship between ISQ and abutment length is the subject of study 5 of the thesis.

Initial ISQ (ISQ at implantation surgery) is a measure of the purely mechanical stabilization of the implant in the bone and is of course related to implant geometry such as width and length. Of clinical concern, it is also related to insertion torque and bone density (Miyamoto, Tsuboi, Wada, Suwa, & Iizuka, 2005; Ostman, Hellman, Wendelhag, & Sennerby, n.d.; Turkyilmaz, Sennerby, McGlumphy, & Tözüm, 2009). If the bone tolerates a high insertion torque, it will initially stabilize the implant more. However, this cannot be translated directly into increased safety for loading the implant. It is true that the high initial ISQ would mean high stability leading to less micro motion, but if this high initial stability comes from over-compression of the bone, it can possibly lead to secondary bone remodeling and resorption, resulting in a decrease in stability and eventual implant failure. However, for an insertion torque that is known not to cause irreversible damage to the bone, a higher initial ISQ will mean higher stability and increased safety of loading.

The ISQ is not a measure of the degree of osseointegration as measured e.g. by the BIC even though in some cases there is a correlation between ISQ and RTQ, and hence BIC (Lars Sennerby et al., 2010). However, an increasing ISQ over time with all other factors held constant means that the total stiffness of the system increases. Since the only known mechanism responsible for changes in bone stiffness is osseointegration, an increasing ISQ will indirectly be a measure of increasing osseointegration.

1.4.2. MEASURES FOR SOFT TISSUE STATUS

Soft tissue inflammation is a complex process that is not easily described with one single clinical measure (Abdallah et al., 2017). Moreover, inflammation may have a multitude of etiologies such that the same macroscopic appearance of an affected area of skin might be due to unrelated pathologic processes. However, there is a need for a clinical measure of the degree of soft tissue reaction around a hearing implant that can somehow summarize the surgical appraisal of the status of the skin, most notoriously whether some kind of intervention is deemed necessary. Such a measure was proposed in 1988 (Holgers et al., 1988), and it has found widespread use in the literature. The scale is described in more detail in Paper 2, and a modification thereof is used in Paper 4.

Examination of the gene expression in the soft tissue around a percutaneous titanium implant revealed that several pro-inflammatory factors are up-regulated at 12 weeks after implantation suggesting a continuous state of immune activation despite lacking clinical signs of inflammation (Calon et al., 2018). This finding is in line with a histologic study also finding evidence for a continuous state of inflammation after implantation (Holgers, 2000). Biopsies taken during episodes of clinical inflammation

(Holgers ≥ 2) showed up-regulation of some pro-inflammatory genes with a positive correlation between the Holgers grade 2 and gene expression (Calon et al., 2018) and between Holgers grade and bacterial colonization (Trobos et al., 2018). Thus, the Holgers scale is at least partly correlated to other, more objective findings of inflammation.

Other soft tissue status measures - namely pain and sensitivity loss - were defined to assess the degree of these complications and will be explained further in paper 2 and 4.

The introduction of skin preserving operation techniques has changed the need for the clinical measure of soft tissue complications, since factors indicating inflammation other than skin appearance (pain, sensitivity loss, skin overgrowth) has become more important due to the overall decrease of skin related issues (I. J. Kruyt, Nelissen, Johansson, Mylanus, & Hol, 2017). Recently the IPS (Inflammation, Pain and Skin height)-scale has been suggested as a new clinical measure of soft tissue complications. This scale can provide a method for more standardized reporting for future research at the same time as serving as a standardized treatment protocol (I. J. Kruyt et al., 2017). However, the scale has not yet been incorporated in reportings from clinical studies (Calon et al., 2018; M. L. Johansson et al., 2018; Trobos et al., 2018).

1.5. CLINICAL RESULTS OF PREVIOUS STUDIES

1.5.1. IMPLANT LOSS AND IMPLANT STABILITY

In general, clinical results regarding long-term stability of the implants have been good. In the earlier years of bone anchored hearing implantation, no objective measurement system to assess implant stability was commercially available. Hence, the clinical endpoint most often reported was implant loss, sometimes supplemented by a notion of stability of the implant as assesses by examination by palpation (Reyes, Tjellström, & Granström, 2000; Tjellström, Granström, & Odersjö, 2007). Furthermore, some patients opt to remove the abutment e.g. due to poor audiological outcome or remitting soft tissue problems. In most cases, the implant will be left in situ and will not be available for further examination unless spontaneously extruded. In other cases the implant will be removed by drilling, in which case it can act as a valuable information source for the basic osseointegration process (Kapsokalyvas et al., 2017; Tjellström, 1985; A. Tjellstrom et al., 1981). In later reports, measurements of ISQ together with figures for implant loss have found widespread use (D'Eredita et al., 2012; Ivo J Kruyt, Nelissen, Mylanus, & Hol, 2018; Wazen, Daugherty, Darley, & Wycherly, 2015).

Implant survival rates have been thoroughly summarized in (De Wolf et al., 2008). Overall survival rates for 10 studies, each including more than 100 implants ranged

from 82.6% to 96.6% with mean follow-up ranging from 0.1 to 6.7 years. For eight studies each including less than 100 implants, survival rates ranged from 93% to 100% with follow-up ranging between 0 and 5 years (mean follow-up could not be determined). A crude total average incorporating study size can be calculated from these numbers giving an overall survival rate of 92.2%. These survival rates are total survival rates, not excluding losses due to trauma, and thus a conservative estimate of the true survival rate. These findings are in accordance with those from a meta-analysis of reports between 2000 and 2011 that found failure to osseointegrate in 0-18% and loss of implant for any reason between 1.6 and 17.4% (Kiringoda & Lustig, 2013)

Survival rates of more specific importance to the implant under study in this thesis are discussed in paper 1-4.

1.5.2. SOFT TISSUE REACTIONS

With the overall good results regarding implant survival, soft tissue reactions constitute the biggest challenge for an overall successful implantation as evidenced by the historical evolution of the surgical methods described in section 1.2. Most reports of soft tissue complications have made use of the Holgers score to describe soft tissue inflammation (M Hultcrantz, 2011; Mylanus & Cremers, 1994; Reyes et al., 2000; Anders Tjellstrom & Granstrom, 1995). However, results have not been consistently reported: some authors have preferred to report the incidence of observations of Holgers grade 2 or higher, since this indicates moderate to severe inflammation that usually needs treatment, while others have reported the distribution of Holgers grade on all five categories. Most authors have reported the proportion of skin reactions to the total number of skin observations. Furthermore, since most studies are retrospective studies without well-defined follow-up intervals, reported incidences may be easily biased: e.g., if a center chooses not to see all patients at regular intervals, but only when they have problems, their results will be negatively biased (De Wolf et al., 2008).

A systematic review of skin complications in all published reports from 1977-2013 found a large inhomogeneity in the reporting standards and the methods used for comparison thus making a meta-analysis impossible. However, there seemed to be a higher complication rate associated with the dermatome technique as compared with the linear incision with soft tissue reduction (Mohamad, Khan, Hey, & Hussain, 2016).

The value of trying to make an estimate for the overall soft tissue reaction incidence could therefore be questioned and possibly only comparisons between studies with comparable follow-up regimes and reporting procedures will reveal important differences. This is done for each of the papers 2 and 4. However, as a guideline, a meta-analysis of reports between 2000 and 2011 found Holgers grade skin reactions

grouped by grades 2-4 ranging from 2.4% to 38.1% with a need for revision surgery in 2.4 to 34.5% (Kiringoda & Lustig, 2013).

CHAPTER 2. AIM AND HYPOTHESES

Based on the available scientific knowledge described in the previous chapter, two clinical studies were designed with the overall aim of investigating the possibility for earlier loading of the bone anchored hearing implant under study, taking into account both issues related to implant stability through osseointegration and soft tissue reactions and evaluating two different surgical approaches. Since one of the central evaluation methods (the ISQ) used in the clinical studies needed further investigation, study 5 was devoted to this aspect.

2.1. PAPER 1

The objectives of study 1:

1. assessment of the initial implant stability of an implant with a moderately rough titanium surface (BIA300, Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden),
2. measuring the implant stability closely in the early osseointegration period to be able to detect a possible damaging influence on osseointegration from early loading,
3. assessment of the progression of implant stability after loading the implant 2 weeks after surgery with one year follow-up, and
4. comparison of the implant stability between two surgical techniques: dermatome technique and linear incision with no soft tissue reduction.

Based on the described relationship between implant geometry and stability, we propose that initial stability will be high. We also propose that this high stability will enable early loading of the implant after two weeks without interrupting the natural process of osseointegration. Furthermore, we propose that stability will continue to increase throughout the osseointegration phase, and finally we propose that stability will settle at a certain level after approximately one year. Factors related to the surgical procedures could influence on initial stability, e.g., the larger sized operation field that arises when using the dermatome technique could influence positively on the possibility for optimal bleeding control, adequate cooling during the drilling, and removal of the periosteum at the implant site. Moreover, if more skin inflammation and epithelial downgrowth occur for one of the surgical procedures this might lead to disturbances in the osseointegration and instability of the implants.

2.2. PAPER 2

The aims of this study are:

1. evaluation of whether loading of the bone anchored hearing implant system BIA300 (Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden) can be safely done after two weeks with regard to soft tissue healing, and
2. comparison of patients operated on with 1) the Linear incision-no thinning (LI-NT) technique or 2) the Dermatome technique with regard to short and long-term soft tissue complications related to inflammation, pain, and sensitivity around the implant site.

We propose that it will be clinically safe to perform processor loading two weeks after the operation with regard to soft tissue healing. We also propose that soft tissue complications will be lower in the group operated on with the LI-NT technique.

2.3. PAPER 3

This study was designed to assess the safety of loading the bone-anchored implant system BI300/BA400 (Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden) 1 week after surgery with the LI-NT technique.

We propose that due to a high initial stability, loading of the implant system after one week will not influence the process of osseointegration, and hence that loading of the implant one week after implantation will be safe regarding the stability and osseo-integration of the implant.

2.4. PAPER 4

The study aimed to evaluate whether a coating with hydroxyapatite on the abutment of a bone anchored hearing implant system (BI300/BA400 (Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden)) would result in fewer soft tissue complications in the first year after implantation when the surgical method was the LI-NT and the implant was loaded one week after surgery compared to patients operated on with the LI-NT-technique and implanted with the implant system BIA300 (Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden).

It was hypothesized that compared with patients operated on with the same technique but with a smooth, as machined, titanium surface implant (BIA300) and hearing processor loading after two weeks, there would be less soft tissue complications around the abutment, possibly due to a tighter bond between the implant and skin.

2.5. PAPER 5

The aim of this study was to investigate the correlation between abutment length and ISQ-value for two bone anchored hearing implant systems (BAHA BIA300, Cochlear

Bone Anchored Solutions AB, Mölnlycke, Sweden, and Ponto Wide Implant, Oticon Medical, Göteborg, Sweden). This was done from

1. direct measurements on human temporal bones and
2. measurements on a curing plaster model

It is known from basic physical principles that the ISQ-measurement is strongly dependent on the abutment length, and we proposed that the measured ISQ decreases approximately linearly with abutment length. In addition, we hypothesized that the dependency could be estimated precisely from measurements on different abutment lengths with the same stability.

CHAPTER 3. SUMMARY OF RESULTS

For the BA300 abutment (Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden) with an as machined smooth titanium surface:

- After surgery with the LI-NT technique, the healing phase progressed with less skin inflammation (Holger's index), pain and sensitivity loss compared to the dermatome technique, probably as a consequence of its less invasive nature.
- During one-year follow-up after loading at two weeks, complications related to inflammation and pain were comparable after BAHS with the LI-NT and dermatome technique, whereas sensitivity loss remained high after operation with the dermatome technique.
- The overall soft tissue complication rate after loading at two weeks was lower than otherwise reported in the literature.

For the BI300 implant (Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden) with a moderately rough titanium surface:

- Loading of the implant at either one week or two weeks did not result in any implant losses during one year of follow-up, and implant stability (ISQ) increased throughout the follow-up period toward a plateau that was reached around one year after implantation.

For the BA400 BAHA abutment with an hydroxyapatite coated surface in the abutment-skin interaction zone (Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden):

- After surgery with the LI-NT technique and loading after one week, the healing phase up to one month progressed with more skin inflammation and pain than what is seen for the same operating procedure using the BA300 abutment and a loading time of two weeks.
- Long term tissue complications was comparable for these two groups, although with a tendency towards more complications in the BA400 group.
- Loading at one week resulted in an acceptable level of soft tissue complications, but it might have burdened the tissue-implant interface with a heavier bacterial load, leading to the overshadowing of a possible long-term positive effect from the hydroxyapatite coating.

For the evaluation of the dependency of the ISQ-measurement on abutment length:

- ISQ was shown to be almost linearly dependent on abutment length (Høgsbro, Gaihede, Agger, & Johansen, 2019)

- The correction for the abutment length was found to be 3.5 ISQ/mm for the implant used in the clinical studies in this thesis.

CHAPTER 4. DISCUSSION

4.1.1. DISCUSSION OF STUDY DESIGN

The overall aim of this thesis was to assess the possibility of earlier loading of a certain implant system than previously advised from a safety point of view. Though it can be argued that including an unloaded healing phase of 4-6 weeks would not pose a big problem for neither patients nor health care system, the positive effects of optimizing the procedure are quite obvious: The patients benefit from the earlier loading from being able to obtain faster hearing rehabilitation, and for those with challenging hearing losses this might lead to fewer days away from work. If loading of the implant and fitting of the hearing processor, which is often done by an audiologist (or audiological assistant), can be scheduled in advance to take place at the same day as the surgical follow-up, the patient will have to schedule fewer leaves from work or other activities. Overall, the shorter loading time will probably lead to fewer visits to the clinic for follow-up during the healing period and the patient can be referred to secondary health care at an earlier time for future follow-up. Also, the advised healing phase is not based on high-level evidence (Snik et al., 2005), and it should be challenged by further scientific investigations. The wish to be able to load the implants at an earlier time was based on scientific evidence and theoretical considerations that it would probably not be harmful to the patients.

In this thesis, three factors are addressed as explaining variables for the outcomes of BAHS: operation technique, implant system design and loading time. An examination of all the possible combinations in a randomized setting would of course be a daunting task, but in an ideal setting, many more arms should be included to be able to fully separate the effects, according to Figure 7. Most notably we did not design investigations for the BA400 abutment using the dermatome technique, since at the time of introduction of the BA400 abutment, the surgical community seemed to loose interest in the dermatome technique, which was considered outdated owing to the good results that were continually being published with the linear incision with or without soft tissue reduction.

Also in widespread use as a bone anchored hearing aid is the Ponto implant (Oticon Medical AB, Göteborg, Sweden). However, at the time of design of the studies for this thesis, these implant was not in use at the Department of Otolaryngology, Aarhus University Hospital, and hence not readily available for clinical studies. This implant system has an as machined titanium surface and an implant diameter of 4 mm (a never design, the Ponto BHX (Oticon Medical AB, Göteborg, Sweden) also has a roughened surface, created with LASER-ablation). A study that directly compares the two different implant systems is an interesting task; however, this was not part of the present study. Furthermore, some possible pitfalls regarding the stability measurements using the ISQ should be addressed before a direct comparison could be

made. As described in paper 5, different SmartPegs are used for the measurements on implant level for the two different implant systems while the same type is used for measurements at abutment level. If a study is to be designed to address the difference in osseointegration for the two implant systems, the differences in absolute ISQ for the two types of implants should be addressed. Only differences in the time-development of ISQ between the two implant systems would be easily available for analysis. However, with the correction factors that are found and described in paper 5, also a direct comparison of absolute stability could be made. As for a comparison of soft tissue issues, this could be more readily performed with the methods applied in this thesis.

The study design of paper 1 and paper 2 was a randomized, prospective clinical study. Randomization is done with the goal of eliminating all known and unknown confounding factors and to be able to use statistics based on random sampling theory (Vandenbroucke, 2004). Therefore, in most cases studying the effect of treatments, it is the design of choice if permitted by ethical, practical and economic considerations. However, if allocation to treatment can be assumed not to be related to outcome, randomization is not needed. For study 3 and 4 we used the design of a prospective cohort study with the same exclusion criteria parameters as in study 1 and 2. If done with no further intentional or unintentional restrictions in the allocation this can also be considered unbiased (Vandenbroucke, 2004) assuming that the consecutive referrals from secondary practice can be considered random.

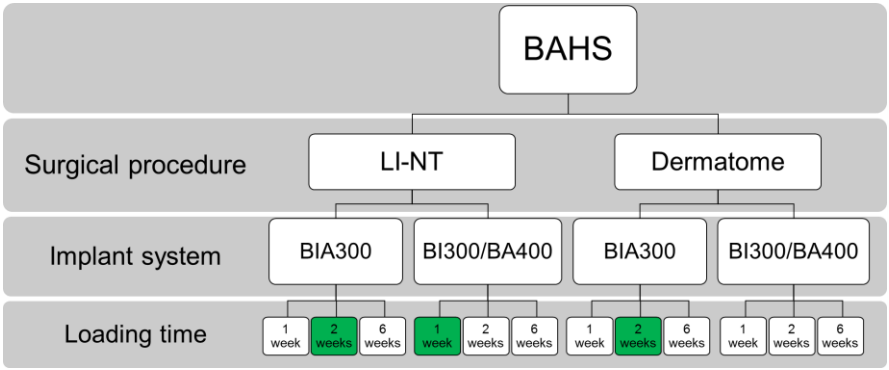

Figure 7 *Diagram showing all possible combinations for comparison of surgical outcome with three factors; surgical procedure, implant system and loading time. Only data for the combinations marked in green are examined in this thesis. BAHS: Bone Anchored Hearing Surgery. LI-NT: Linear incision, no thinning. Implant systems are explained in the main text.*

In paper 3 and 4 we are seeking to make inferences about the influence from both loading time and implant system. However, we do not have separate data for the loading time (one vs. two weeks) with the same type of implant system (BA400) nor for the implant system (BA300 vs. BA400) variable with the same loading time (one week). An alternative to the study design chosen in paper 3 and 4 would of course be

a (randomized) study with an arm including a loading time of 2 weeks with the BI300/BA400 system to be able to separate the effect of the loading time variable. We have argued in paper 4 that the effect of the surface coating from the BA400 abutment would not have a large effect during the initial healing phase, whereas it would be expected to dominate the results during longer term follow-up, so that differences in outcome during the early healing phase are more ascribed to loading time whereas longer term results are more ascribed to surface coating. This is questioned in a recent article, since early colonization of the abutment surface might lead to longer term influence as well (Kapsokalyvas et al., 2017). However, we believe that we have formulated the conclusions from our studies so they are not subject to bias although future designs could preferentially take this potential conflict into account.

The scheduling of follow-up visits allowed for a very thorough assessment of the progression of stability of the implants, especially for paper 1, in which the initial healing phase up to one month was monitored by 7 clinical visits and ISQ measurements. The findings in both paper 1 and 3 showing a monotonously increasing ISQ contradicted earlier reports indicating a possible vulnerable period during the osseointegration phase (Dun, de Wolf, et al., 2011; Mierzwinski et al., 2015), where an initial stability dip was noted even though the implants had not been loaded at this time. One possible explanation for this could be a difference in insertion torque that has led to a higher initial stability though we do not have data to support this.

The control group for study 3 and 4 was the patients operated on in study 1 and 2, and study 3 and 4 therefore corresponds to adding one of the missing arms in the diagram in Figure 7. This was done outside of randomization thus increasing the possibility of bias. However, all operations were done by the same surgeons in the same proportion and with a relatively short time span between the studies, so that the overall setup was essentially the same.

Sample size calculations in Paper 1-4 were based on assumptions concerning implant stability since this was the variable most easily suited for comparison with other studies. Of course, a formal sample size calculation could have been carried out also for the expected difference in distribution of Holgers score, pain and numbness, but these numbers vary much more in the literature, making it hard to find a useful estimate (Kiringoda & Lustig, 2013). The sample size would then have been based on the larger of the minimal sample size calculation.

4.1.2. DISCUSSION OF METHODS

4.1.2.1 Comment on statistical methods for paper 1:

In the statistical analysis of the ISQ data for the two surgical groups a number of t-tests were used to show that there was no difference between the two groups in the mean ISQ at any of the time points (paper 1, table 3). However, this simple approach

disregards that the repeated measurements for the same subjects are generally correlated, and therefore not independent. This is a well known complexity when dealing with longitudinal data. One method to circumvent this complexity in the data is to construct a univariate summary variable for each patient, which was done via the "area under the curve" (AUC) that was formally analyzed in the article.

However, the most general approach to a formal statistical analysis of the data is to make a non-linear mixed effects regression model. Since the stability, and hence the ISQ, can be expected to grow towards some asymptotic maximum, the ISQ can be argued to follow a differential equation of the form

$$ISQ'(t) = constant - ISQ(t)$$

where *t* is the time. ISQ as a function of time will therefore have the general functional form

$$ISQ(t) = asymp + (R0 - asymp)Exp(-c * t)$$

where *asymp*, *R0* and *c* are constants.

A mixed model fit to this model takes into account the variability between patients in all three parameters of the model and can furthermore test for difference of the surgical method. Together with an independent statistician, this analysis was carried out and a log-likelihood test showed that there was no difference between the time development of the ISQ between the surgical groups (p = 0.92).

4.1.2.2 Comment on statistical methods for paper 2:

The analysis of the ordinal data for Holger's index, pain, and sensibility loss presented in tables 2-4 makes use of a number of comparisons via the Wilcoxon rank sum test with correction for ties and the chi-squared test for the accumulated data as described in the article. However, a more general approach using ordinal regression with a cumulative link mixed model can more adequately be used to test for a difference between the two surgical models, incorporating all data points at once and taking into account the longitudinal nature of the data that leads to correlation between measurements for the patients at different time points. This regression model analysis was carried out together with an independent statistician and showed that the overall result for Holger's score was indeed different for the two surgical groups (p = 0.023[1]).

[1] After publication of paper 2, we discovered that one value for patient 32 at time = 90 days for the Holger's index was erroneously entered as 2 in stead of the correct value "N/A". The correction of this changed the overall p value from 0.010 to 0.023. A supplementary analysis has also been carried out for the Wilcoxon rank sum test which changed the stated p-value from 0.195 to 0.37, hence not changing the inferential conclusion.

For pain and sensitivity loss, there was also a difference between the groups in the overall regression analysis ($p = 0.049$ (pain) and $p<10\text{-}6$ (sensitivity loss)). The more elaborate statistical model therefore leads to the same overall conclusions that were presented in the paper.

4.1.3. DISCUSSION OF RESULTS

4.1.3.1 Operation technique

A systematic review on complications of tissue preservation surgical techniques from 18 articles (including paper 2 from this thesis) found that all authors reported superior or similar outcomes from tissue preservation techniques compared with a variety of tissue reduction techniques (Verheij et al., 2016) with complication rates very much comparable to the ones found in paper 2.

In a retrospective comparison of 132 patients between the dermatome technique and the linear incision with soft tissue reduction and a median follow-up of 47.5 months, no differences between Holgers ≥ 2 (20.5% (dermatome) vs. 21.6% (linear)) was found; however, more skin thickening was found in the dermatome group (Strijbos, Bom, Zwerver, & Hol, 2017).

Blood flow is better in the skin after tissue preservation technique than after tissue reduction technique measured with laser-Doppler flowmetry (Jarabin et al., 2014) which can be hypothesized to be an explanatory factor for the superiority of the non-soft tissue reduction techniques.

A newly published study has found comparable, excellent results for three year follow-up data on 25 + 25 patients operated on with the linear technique with and without soft tissue reduction with regard to most clinical measures apart from sensibility where the technique without tissue reduction was superior (Ivo J. Kruyt et al., 2019). Nine out of the 25 patients operated on with the non-tissue reduction technique and 3 patients in the soft-tissue reduction group experienced a Holger's score of ≥ 2 during the 3 years follow (not significant) with only two patients in the reduction group needing revision surgery.

4.1.3.2 Coating

As discussed in section 1.3.2 and reviewed in (Abdallah et al., 2017), efforts to find a way to eliminate inflammation around a skin penetrating device have been long lasting and hitherto not successful.

The basic idea behind the coating is to obtain better adherence between soft tissue and abutment. This seems to work in some cases since in a histologic study of an abutment removed from a patient some direct adherence was formed at the level of the dermis

as evidenced by the finding of structured skin on the surface of the abutment (van Hoof et al., 2015). Lately, indications that a tight connection is formed between implant and skin has been found using two-photon microscopy of markers for specific adherence structures of 4 abutments retrieved from patients (Kapsokalyvas et al., 2017).

Our results indicated that the hydroxyapatite coating on the BA400 abutment does not lead to a significant reduction of skin inflammation in a clinical setting. There was a non-significant trend toward a negative influence from the coating although at a low and acceptable level. These results for the soft tissue complications raised the question whether the coating of the surface with hydroxyapatite actually leads to more complications? One early report from an animal study in dogs noticed a strong tendency for infection around a percutaneous device when coated with porous HA (pore size 50-150µm) but not with dense HA (pore size 1-2 µm) (Shin & Akao, 1997), so the possibility exists that coating the surface with a relatively porous material such as the HA might have the opposite effect as what was intended.

Clinical evidence on this issue is conflicting: A case report of 7 consecutive patients implanted with the BA400 abutment has shown infection in all cases during a follow-up of 7 months with only two of the patients still using the abutment after one year (Malou Hultcrantz, 2017). One retrospective series of 16 patients found worst Holgers grade 2 in three patients (18.75%) or in 5.1% of the total visits (loading time: 4 weeks) (Iseri et al., 2015). Thirty consecutively operated patients with a minimum follow-up of six months found only one patient having a Holgers score of 2 and one patient having a Holgers score of 3 during the follow-up (Wilkie, Chakravarthy, Mamais, & Temple, 2014).

In a retrospective cohort study with 26 BA400 abutments there was skin thickening in 34.6% compared to 9.4% out of 26 implants with a smooth titanium surface (Ponto Wide Implant, Oticon Medical AB, Göteborg, Sweden). Four of the BA400 implanted patients needed revision surgery versus 2 of the Ponto implants (median follow-up 16.5 months) (van der Stee, Strijbos, Bom, & Hol, 2018). With a modified punch technique and a follow-up time of 3-7 months, a maximum of Holgers grade 2 was noticed in 2 out of 6 patients in another retrospective survey (Alshehri, Alsanosi, & Majdalawieh, 2016).

A randomized clinical trial of the BA400 (operation technique: LI-NT) vs. BA300 (operation technique: LIT-r) (Cochlear Bone Anchored Solutions, 2018) show no significant differences in Holgers score with 15/51 (29.4%) patients with the BA400 having had a maximum Holgers score ≥ 2 vs. 12/52 (23.1%) in the BA300 group during one year of follow-up. Also, a combined endpoint of local adverse events, combining infection/inflammation, overgrowth, pain, and numbness (between 3 weeks and 1 year) was evaluated with a non-significant lower mean score for the BA400 implant (Cochlear Bone Anchored Solutions, 2018).

4.1.3.3 Loading time

No studies have been published since paper 1 and 3 that focuses on evaluating implant stability after loading at one or two weeks. One study of implant stability and losses in children reports two patients loaded at one and two weeks with good result, the rest were loaded after at least four weeks (McLarnon et al., 2014). Another study on children with the BI300 implant and a mean loading time of 7.5 weeks (range: 2-14 weeks) found an increasing ISQ-curve with a small initial dip after 7-10 days (Mierzwinski et al., 2015).

Five year follow-up data from a randomized trial between BA210 and BIA300 with loading time from 6 weeks showed a continually higher ISQ for the BI300 implant with equal survival rates in the two groups (not related to explantation) of around 95% (Den Besten et al., 2016).

Although no formal consensus statement has been published, a loading time of two weeks has become the recommendation from the manufacturing company (Wigren, 2016).

4.1.3.4 ISQ dependency on abutment length

The study of the dependency of the ISQ measurements on abutment length was undertaken to solve the problems, stated in the literature, about comparing measurements made on the same implants with different abutment lengths (Ivo J. Kruyt et al., 2019; Nelissen et al., 2015) which is impossible without the results from this study. The results in this thesis were obtained by a direct empirical examination of the relationship which is the method that most directly can be carried over to clinical application – of course with the cost of the random error uncertainty that is always present in empirical data. However, by the combined use of both a human cadaveric model and a model in which measurements are made on the implants while inserted in hardening (curing) plaster this uncertainty was diminished to a level that was smaller than both the level of uncertainty associated with the use of different SmartPegs and the uncertainty associated with clinically relevant uncertainty in fastening torques of the SmartPegs. This uncertainty is stated by the manufacturer to be as large as 5 ISQ (Osstell, 2019), and the 95% confidence intervals of the coefficients of abutment length dependency in this thesis is about 0.3 ISQ (Paper 5). No other studies exists that directly examines this relationship. An early paper (L Sennerby & Meredith, 1998) mentions the dependency of abutment length to be around 2-3 mm; however, this dependency was measured with an earlier type of measurement device not making use of SmartPegs, but individually calibrated transducers, and the measurements were not undertaken on the bone anchored hearing implants used today. Since the resonance frequency of an implant system must be hypothesized to be strongly dependent on geometry and mass distribution, results to

be used in a clinical setting should be obtained specifically on the type of implant system.

The study was originally planned to incorporate the development of a mathematical model for the examination of the theoretical dependency of abutment length on ISQ. This could probably be carried out by a finite element analysis of the partial differential equations governing the vibrations of the system as has been done for dental implants to investigate the dependency of varying degrees of osseointegration on the resonance frequency (Deng, Tan, Liu, & Lu, n.d.). Even though such a method could probably be used to predict the dependency, it would not be possible to adopt the findings in a clinical setting like the direct measurements presented in the thesis and the model was therefore not carried out.

CHAPTER 5. CONCLUSIONS AND PERSPECTIVES

The use of percutaneous implants as a basis for hearing rehabilitation via bone conducted sound is a safe and overall successful procedure. This thesis has investigated some of the aspects that influence the success in adults, which are otherwise healthy and has expected normal bone quality. For children, some specific issues are important in evaluating the success of the implantation and the post-implantation development. For young children, the thickness of the scull is still not in general a full 4 mm as needed for the implantation of a 4 mm long implant and a 3 mm implant can be used in stead with the cost of loss of some intrinsic stability. The bone remodeling rate, on the other hand, is faster in children and osseointegration may therefore be expected to proceed faster in children than in adults. The results from this thesis can therefore not be carried directly over to recommendations for the operation on children. For the post-implantation regime as well, at least two points of major concern influence the difference in outcome between children and adults. Most notably, children has a higher rate of traumatic incidents that might disrupt the osseointegration of the implant and they need help to assure optimal hygienic control of the abutment and skin. It therefore seems obvious that to optimize the results for children, a larger degree of osseointegration and skin healing should be obtained before loading the implant. The interesting and important field of pediatric implantation constitutes a research field of its own.

A rapid development over the last years has given rise to a range of other choices of bone conducting devices for patients with complicated mixed hearing loss. However, the percutaneous implants will probably still have a large share of the chosen options due to the easy and fast surgery, the relatively low cost compared with more elaborate solutions, and the development of the sound processors that assure better hearing rehabilitation even in the presence of a sensorineural hearing loss. Therefore, it is still of concern to optimize the outcome of the operation. It seems that with the state of the art implants on the market now, the challenge of designing a stable implant that will be osseointegrated has been solved. As was documented in this thesis, the implants can be loaded even after one week without an increased risk of extrusion.

When the implant is stable and the hearing processor is well-functioning, the remaining issue for the patients is how much inflammation and pain at the implant site they experience. Even though the numbers for serious skin inflammation and infection are low, for the life span of an implant any patient may have some annoying periods that need attention and possibly treatment of some kind, albeit in most cases only local treatment with ointment that can be prescribed by their own doctor or an ENT-specialist working in secondary health care. So, the most important area within

this field is therefore the implant-skin interaction and how to control inflammation and avoid infection. The only implant system available today that has a specific coating to counteract infection around the abutment is the BA400 that has been examined clinically in this thesis. This coating has not been able to make drastic changes to the level of peri-abutment inflammation; rather, in our investigations, it seems to increase the amount of inflammation slightly. The pore size of the hydroxyapatite plays a large role and the balancing between optimal skin adherence and bacterial control is probably not reached yet. It is also possible that other coatings could prove better in this aspect. The development needs the attention from basic research laboratories with skilled material engineering staff. Hitherto, the development has mostly been driven by the manufacturing companies, probably due to the costly process of translating possible developments into clinical use.

The interplay between the abutment coating and the surrounding skin is further influenced by the microbiota that exists in the interface. The composition of this mikrobiota is probably influenced by both the loading time of the implant, patient specific factors such as tissue type, bacterial load, and hygienic control. It can be hypothesized that for some patients, the HA-surface gets colonized early with pathogenic bacteria and that the rougher surface on a coated abutment makes it more difficult to remove these pathogens compared with a smooth surface.

The best way to clinically assess the stability of an implant remains controversial. The method used in this thesis was based on resonance frequency analysis of the implant-abutment system and is very easily applicable in the clinical setting. However, there is no consensus on which level of ISQ it should be considered safe to load the implant. Two main issues exist that should be addressed to this end. First, since the ISQ-reading reflects the density (and thereby the Young's modulus) of the surrounding bone, different patients will have different ISQ-readings for totally osseointegrated implants due to differences in their bone density. This means that a situation could appear where two different patients at some point in time can have the same ISQ-reading for their implants even though the degree of osseointegration can deviate largely. The first patient might have very dense bone but only limited osseointegration and the second patient might have less dense bone but total osseointegration. In the first patient, loading of the implant may lead to excessive micro motion, eventual fibrous healing in stead of osseointegration, and possibly loss of the implant, whereas for the second patient, loading of the implant might not lead to excessive micro motion thus not disturbing the bone remodeling, since it is already complete and therefore less prone to disturbances. Because of this inherent feature, it is hard to imagine that one can identify a certain number above which loading of the implant is safe. At least, this endeavor should probably be limited to the ISQ measurement at the time of implantation, since at this time, it is known that only primary stability is acting and that osseointegration has not taken place. Hence, the expected amount of micro motion can possibly be better estimated from this initial measurement. Of course, all attempts to obtain such a clinically useable number should account for the differences

in abutment length and calibration of the SmartPeg as demonstrated in this thesis. The patient specific time development of ISQ remains the best measure for each patient, since the changes in ISQ reflects changes in the stabilizing forces in the bone, and a large decrease in ISQ in the healing phase may indicate that a longer healing time is needed before loading.

The surgical procedure used for the implantation continues to develop. Oticon Medical has few years ago launched an implant system together with a specific surgical procedure in which no incision is necessary (the Minimal Invasive Ponto Surgery (MIPS)-technique). This technique is one out of several techniques making use of only a punched hole that has been published (punch-techniques). With the punch-techniques, a hole approximately 5 mm in diameter is punched in the skin all the way to the cranial bone and the periosteum is removed while all other soft tissue is left intact. With the MIPS-technique, drilling is done through a specifically designed cannula and the implant is inserted as usual. For the other techniques, more ad-hoc solutions are used while drilling to protect the soft tissue from frictional heating from the burr. It seems that the major steps in surgical procedure was taken mainly when the community moved from the use of flaps or grafts to only local incision and with the introduction of the technique without reduction of soft tissue. Although possible, it seems that the procedure cannot be optimized substantially by the introduction of the punch techniques, since both the linear incision without soft tissue reduction and the punch technique essentially leaves the subcutis intact regarding its immune competency and healing capacity, although it might be slightly better with the punch techniques. Hence, in stead of pursuing optimization of the surgical procedure which is already very fast and safe, I propose to spend more research efforts on understanding the interplay between abutment and skin which holds the key to eliminating tissue inflammation in the long term perspective.

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APPENDICES

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-430-0

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